New and Notable

Magnesium Selective Ion Channels

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The homeostasis of intracellular ion concentrations within physiological limits is one fundamental characteristic of any living organism. Magnesium, an alkaline earth metal, is well known to stabilize macromolecule structure and to participate as an essential cofactor in many enzymatic reactions. These tasks apparently require a total cellular concentration between 14 and 20 mM, and a free concentration at ~0.3–1.5 mM, the highest for the physiologically relevant divalent cations. Information on proteins that regulate Mg^{2+} homeostasis in cells is, however, very limited, presumably because due to its large free concentration, it had been originally assumed that no major concentration changes are required for Mg^{2+} to mediate its cofactor role. Therefore, most research was focused on the second messenger role of Ca^{2+}, and not much effort was put forth to develop suitable tools to accurately measure Mg^{2+} oscillations in cells. Our understanding is moving on rapidly now, as a number of recent reports brings to light that the cellular content of Mg^{2+} varies upon stimulation and in doing so, modulates cell functions, as it was initially proposed by Maguire (1,2).

In bacteria, magnesium uptake is mainly mediated by the CorA family of membrane proteins of which the ortholog from *Thermotoga maritima* has been recently crystallized, revealing an unprecedented fold (3). In addition, several functional CorA homologs have been identified in the inner mitochondrial membrane of yeasts and mammals (Mrs2/Lpe10 family) as well as in the plasma membrane of yeast (Alr family). Despite very low sequence similarity, usually no more than 10% of overall sequence identity, mainly centered around the YGMN core motif at the end of TM1, individual proteins can functionally complement each other over large phylogenetic distances (4). In mitochondria, Mrs2p proteins have clearly been shown to mediate Mg^{2+} uptake and have been therefore referred to as the major magnesium influx system. Nonetheless, a detailed electrophysiological characterization of these Mg^{2+} transport systems was clearly lacking until the article by Schweyen and co-workers in this issue (5).

For the very first time, they fully characterized the electrophysiological properties of a Mg^{2+} selective channel, Mrs2p, a high conductance (155 pS) channel measured by patch-clamp of giant liposomes fused with sub-mitochondrial particles expressing tagged Mrs2p. Mrs2p is shown to be primarily selective for Mg^{2+} and permeate to a lesser extent Ni^{2+} (45 pS) whereas it is able to discriminate against Ca^{2+}. From the point of view of a cell, this is as selective as you want to be regarding divalent cations, and it is quite likely that the nickel permeation may not have any physiological relevance. In agreement with their previous bulk Mg^{2+} transport assay using Mag-Fura-2 as an Mg^{2+} fluorescent probe, the ionic currents were abolished in the presence of the structural analog of the fully hydrated Mg^{2+} ion, Co^{III}-hexamine, on the extracellular side. Co^{III}-hexamine is also a potent inhibitor of CorA-driven Mg^{2+} uptake in bacteria. Its ability to inhibit uptake has been interpreted as suggesting that both transport systems (Mrs2p and CorA) initially bind a fully hydrated cation.

If we are left without a clear understanding of what makes these transport systems so unique and selective for Mg^{2+}, we can perhaps go back to basic physical chemistry. Indeed, to appreciate the selectivity of Mrs2p and related channels, one must consider the cation's peculiar physical nature (6). Mg^{2+} is the most densely charged species of the biologically relevant cations, and while the unhydrated Mg^{2+} has the smallest diameter (0.65 Å), the fully hydrated cation (5.0 Å) is the biggest of all. Mg^{2+} is known to interact very strongly with surrounding molecules—always hexacoordinated in a very rigid and spatially defined manner, a fact that highlights why evolution has chosen this ion to very precisely position water molecules or ATP in the catalytic site of enzymes. Any relationship to the proposed mechanism for K^+ and other monovalent cation selectivity, in which the cation is largely dehydrated upon initial interaction with the channel, seems counterintuitive here as the strength of the Mg^{2+}-protein interaction would not favor a high throughput such as reported in the study by Schweyen and co-workers (5). For magnesium selective channels, it is possible that the selectivity does not arise from the optimal spatial coordination of a naked ion within the core of a selectivity filter, but rather from the initial interaction of the hydrated Mg^{2+} ion with the hypothetical binding loop between TM1 and TM2 (the most conserved motif). In such a scenario, the significantly smaller hydrated Ca^{2+} would not be able to bind to the channel with sufficient affinity. Remarkably, Mrs2p and CorA orthologs lack negatively charges residues within their membrane domain, implying that Mg^{2+} influx occurs without a single electrostatic interaction.

If the mechanism of ion selectivity and permeation are still highly elusive at the moment, the work presented here provides useful insight on the nature of the gating activator. Indeed, the authors demonstrate that Mrs2p open probability (NPo) is lowered from 60 to 20% when 1 mM of Mg^{2+} is present in the matrix side, suggesting that Mrs2p is gated by a negative feedback mechanism. The structure of *T. maritima* CorA showed Mg^{2+} bound in the cytoplasmic

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domain, between Asp^{89} from one monomer and Asp^{253} from the adjacent monomer, suggesting that a negative feedback mechanism is likely to occur also for CorA, but obviously, more definitive structural data are required (3,7,8).

From the landmark work of Schweyen's group, it appears probable that CorA may catalyze Mg^{2+} uptake by acting as a channel driven by the inward electrochemical gradient of Mg^{2+}. From the picture described here, it comes into sight that elucidating the basic electrophysiological properties of CorA could bridge the gap between the functional data on magnesium channels and their structure and would provide an ideal stage for experimental and computational biophysicists to expand our understanding of magnesium selectivity and conductivity.

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